Anomalies of the *TCF2* Gene Are the Main Cause of Fetal Bilateral Hyperechogenic Kidneys

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Prenatal discovery of fetal bilateral hyperechogenic kidneys is very stressful for pregnant women and their family, and accurate diagnosis of the cause of the moderate forms of this pathology is very difficult. Hepatocyte nuclear factor-1β that is encoded by the *TCF2* gene is involved in the embryonic development of the kidneys. Sixty-two pregnancies with fetal bilateral hyperechogenic kidneys including 25 fetuses with inaccurate diagnosis were studied. *TCF2* gene anomalies were detected in 18 (29%) of these 62 patients, and 15 of these 18 patients presented a complete heterozygous deletion of the *TCF2* gene. Family screening revealed *de novo TCF2* anomalies in more than half of the patients. *TCF2* anomalies were associated with normal amniotic fluid volume and normal-sized kidneys between −2 and +2 SD in all patients except for two sisters. Antenatal cysts were detected in 11 of 18 patients, unilaterally in eight of 11. After birth, cysts appeared during the first year (17 of 18), and in patients with antenatal cysts, the number increased and developed bilaterally with decreased renal growth. In these 18 patients, the GFR decreased with longer follow-up and was lower in patients with solitary functioning dysplastic kidney. Heterozygous deletion of the *TCF2* gene is an important cause of fetal hyperechogenic kidneys in this study and showed to be linked with early disease expression. The renal phenotype and the postnatal evolution were extremely variable and need a prospective long-term follow-up. Extrarenal manifestations are frequent in *TCF2*-linked pathologies. Therefore, prenatal counseling and follow-up should be multidisciplinary.

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With the development of prenatal ultrasonography, obstetricians and pediatric clinicians increasingly are facing the challenge of counseling pregnant women. Prenatal diagnosis of bilateral hyperechogenic kidneys is a difficult situation because (*1*) fetal sonography alone fails to provide an accurate causative diagnosis, (*2*) within each etiologic group is a wide range of outcomes, and (*3*) there are only a few fetal markers with unfortunately low predictive value of postnatal renal function. The identification of fetal renal abnormalities may be extremely stressful for the parents and devastating when termination of pregnancy is indicated.

The most frequent causes of fetal hyperechogenic kidneys are autosomal recessive polycystic kidney diseases (ARPKD), autosomal dominant polycystic kidney diseases (ADPKD), and cystic dysplasia. The remaining causes include transient hyperechogenicity, tubulopathies, tuberous sclerosis, tubular dysgenesis, and miscellaneous diseases (1).

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The outcome of fetal hyperechogenic kidneys can be predicted only in the most severe forms, ascertained by severe oligohydramnios and kidney enlargement. For less severely affected patients, the long-term outcome is difficult to predict, and no appropriate fetal analysis is able to predict the long-term renal function. Abnormal fetal serum β2-microglobulin and cystatin C values are associated with poor postnatal renal function, but normal values do not exclude postnatal renal failure (2).

Hepatocyte nuclear factor-1β (HNF-1β) is a structurally related member of the homeodomain-containing superfamily of transcription factors. HNF-1β functions as homodimer or heterodimer (3). It plays a role in the tissue-specific regulation of gene expression in various organs (4), including the liver, the kidney, the intestine, the genital organs, and the pancreas (5). They also are involved greatly in the embryonic development of these organs. This transcription factor is encoded by the *TCF2* gene. Heterozygous mutations in this gene were described initially in a monogenic form of diabetes, type 5 maturity-onset diabetes of the young (MODY5) (6). It is characterized by an autosomal dominant inheritance and a nonketotic diabetes as a result of a primary defect of insulin secretion (7).

A wide clinical spectrum of renal morphologic and structural manifestations and functional abnormalities have been associ-

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ated with *TCF2* mutations: Familial hypoplastic glomerulocystic kidney disease (8–10), cystic renal dysplasia (11), solitary functioning kidney (12), oligomeganephronia (13), cystic kidneys (14), enlarged collecting systems, atypical juvenile hyperuricemic nephropathy (15), and horseshoe kidney (16,17). *TCF2* adult patients have mild to moderate renal failure in the absence of diabetic nephropathy (18). Moreover, pancreatic atrophy, urogenital abnormalities, abnormal liver enzyme levels, and hyperuricemia are observed in patients with *TCF2* mutations (12–14,19,20).

Prenatal forms also were described but only as a case report: Cystic renal dysplasia (8,9,12,16), bilateral hyperechogenic kidneys (14,21), renal agenesis, pelvicaliceal dilation, and multicystic dysplastic kidney (14). More recently, a pediatric phenotype related to *TCF2* mutations had been reported in a large cohort (22).

To date, more than 40 different *TCF2* mutations and large heterozygous deletions (22,23) associated with distinct renal disorders have been described. The physiopathologic mechanism of the *TCF2*-related renal disease is not understood clearly. HNF-1β seems to be important starting from the earliest induction phases of kidney development. HNF-1β–deficient mouse embryos die at embryonic day 7.5 as a result of a defective differentiation of the extra embryonic visceral endoderm (6). HNF-1β expression also has been demonstrated in fetal human metanephric kidneys (24).

We studied the implication of *TCF2* gene anomalies in a population of 62 newborns or fetuses with antenatally diagnosed hyperechogenic bilateral kidneys. We showed that large genomic deletions in the *TCF2* gene are the most frequent cause of antenatally diagnosed hyperechogenic bilateral kidneys. These findings may have major implications in prenatal counseling and tailor-made follow-up of these young patients.

Materials and Methods

Patients

Between 1987 and 2005, bilateral fetal hyperechogenic kidneys were diagnosed in 62 pregnant women in the Prenatal Diagnosis Department in our hospital. One patient was identified as a result of a familial history of autosomal recessive disease tubular dysgenesis, three patients because of a family history of dominant polycystic kidney disease, one patient with family history of dominant glomerulocystic kidney disease with diabetes, and one patient with familial hypoplastic cystic kidney disease. In the 56 other cases, abnormal fetal kidneys were discovered by routine ultrasonography.

Additional anomalies were ruled out on the basis of ultrasound and fetal karyotyping. Associated anomalies were confirmed by postnatal or postmortem examination.

Fetal kidneys were considered hyperechogenic when their echogenicity was greater than that of the liver. The size of the kidneys was expressed as SD above or below the mean derived from the growth charts of Le Guern *et al.* (25). The presence of cysts in the fetal kidneys and their localization in the cortex and/or the medulla were determined.

The amount of amniotic fluid was assessed by a semiquantitative method. Oligohydramnios was considered when the amniotic fluid index was <5 cm. Amniotic fluid index is described as the sum of the vertical of the largest pockets of the amniotic fluid in the four quadrants of the uterus. Severe oligohydramnios corresponded to quasi-anamnios when the largest single pocket of amniotic fluid was 2 cm or less.

According to standard procedures, fetal treatment was based on the assessment of amniotic fluid volume, kidney size, and sometimes the fetal serum β2-microglobulin concentrations. Fetal renal failure was defined when the fetal serum β2-microglobulin concentration was >5 mg/L and considered severe when the level was >7 mg/L (2,26). Termination of pregnancy (TOP) was conducted after parental request in cases with severe oligohydramnios or when the kidney size was >2 SD with an elevated fetal serum β2-microglobulin concentration. In the other cases, parents were encouraged to continue the pregnancy. After the prenatal counseling with obstetricians and pediatric nephrologists, parental autonomy was respected as for continuing or terminating the pregnancy. Postmortem histologic examination was performed in all cases of termination of pregnancy or after neonatal death.

Postnatal Clinical Investigation

After birth, all of the surviving infants were followed regularly by the pediatric nephrology unit. Sonography examinations were performed in the same center. The following parameters were analyzed: Renal cysts, hyperechogenicity, hypoplasia (kidney length), pelvic dilations, and other structural anomalies. Renal cysts were divided into cortical and medullary cysts and into two subgroups: Microcysts (<10 mm) and macrocysts (>10 mm). Poor corticomedullary differentiation and/or diffuse hyperechogenicity was in favor of renal dysplasia. Renal hypoplasia was defined as a kidney length of <2 SD for age; renal enlargement was defined when kidney length was >2 SD (27).

For patients who were positive for a *TCF2* gene anomaly, we determined serum creatinine levels, serum levels of hepatic enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], and γ-glutamyl transferase [GGT]), blood glucose levels, and urate levels and fractional excretion. We also performed a lipidogram. GFR was estimated using the Schwartz formula. An estimated GFR <70 ml/min per 1.73 m^2 was considered as renal failure <40 ml/min per 1.73 m^2 as severe chronic renal insufficiency. Serum levels of hepatic enzymes (AST, ALT, and GGT), pancreatic enzymes, blood glucose, insulin, and glycosylated hemoglobin levels were analyzed using standard methods. We did not use biologic values that were obtained before the age of 3 mo to avoid misinterpretation of early creatinine values. For all children, these analyses were performed without infection, dehydration, or other pathologic conditions that might interfere with renal function or other study parameters.

All parents gave written informed consent for their children. Parents were screened systematically by ultrasound for renal cysts that were suggestive of ADPKD, autosomal dominant glomerulocystic kidney disease, and *TCF2* in the case of children with *TCF2* anomalies.

Molecular Analysis

We proposed and performed a screening for *TCF2* gene mutations in patients with cortical microcysts or isolated hyperechogenicity, with glomerular cysts at the fetal or postmortem examination or when no accurate diagnosis was established. Two molecular strategies that consisted of quantitative multiplex PCR amplification of short fluorescence fragments (QMPSF) for the search of large genomic arrangements and sequencing for the detection of base pair substitutions or small insertion/deletion were performed sequentially in 23 probands. When a *TCF2* gene anomaly was identified in a proband, affected siblings were screened for the same *TCF2* anomaly. Furthermore, *TCF2* gene anomaly screening was offered to parents whatever their clinical status.

QMPSF that is based on the use of a limited number of PCR cycles enables the detection of gross genomic rearrangements. We applied this

method to exons 1 to 8 of *TCF2* gene. PCR amplification conditions and QMPSF analysis were done as described previously (23).

Patients without *TCF2* rearrangements then were screened by direct sequencing. The minimal promoter, the coding regions, and exon-intron boundaries of *TCF2* gene were screened for mutations by direct sequencing as described previously (6).

Results

Patients' Antenatal Characteristics

We studied 62 patients from 56 unrelated families. The main prenatal characteristics of the patients with ARPKD diagnosis are summarized in Table 1, with ADPKD in Table 2 and various diseases in Table 3. Four patients presented a tubulopathy (data not shown). Antenatal data of the patients with imprecise diagnosis are summarized in Table 4 ($n = 28$). Among them, 25 were screened for mutations in *TCF2* gene. We found 16 unrelated patients and two siblings with *TCF2* gene anomalies, together representing more than one quarter of our cohort. Patient 26, even with a family history of glomerulocystic kidney disease with MODY in the father and the grandmother was not considered to have a *TCF2* gene anomaly because of parental refusal for genetic exploration. Seven children were without known *TCF2* gene anomaly.

The fetal β2-microglobulin serum concentrations were measured in four fetuses with a *TCF2* gene anomaly. The values were in the limit range: For patient 4, 6.3 then 6 mg/L (21 d later) because of left multicystic kidney with right hypoplastic kidney and normal amniotic fluid; 2.8, 5.0, and 4.9 mg/L for patients 9, 10, and 14, respectively. For these four patients, pregnancies were continued.

Eighteen TOP were performed: 10 in the ARPKD group, two in the ADPKD group, and seven in patients with renal dysplasia. Criteria for TOP were moderate or severe oligohydramnios and kidney enlargement (>2 SD) with poor corticomedullary differentiation. Two fetuses with oligohydramnios and glomerulocystic kidney disease that led to TOP were tested and found to be negative for *TCF2* gene anomalies.

TCF2 Molecular Analysis

Twenty-five patients (23 probands and two relatives) who fulfilled our selection criteria accepted and were screened for *TCF2* alterations. Two strategies using QMPSF for the search of large genomic rearrangements and sequencing for the detection of base pair substitutions or small insertion/deletion were performed on unrelated patients ($n = 22$). A heterozygous molecular alteration of *TCF2* was found in 16 probands and two relatives. Among these patients, the complete deletion of *TCF2* (M1_W557del) was detected in 15 of them. The size of the deleted region was estimated to 1.2 megabases by genotyping of neighboring microsatellite markers and single- nucleotide polymorphisms as described previously (23). A single-exon deletion of exon 4 (R270_G349del) was identified in one proband (patient 10). Besides these deletions, which affect the majority of the patients, two different mutations were identified. One novel mutation (patient 12) is an amino acid substitution (Q253P) that is located in the DNA-binding domain and affects a residue that is conserved in HNF-1β sequences of different species. One mutation, IVS6 + 1G>A, a novel base pair substitution, affects the splice donor site of intron 6 (patient 14).

When a *TCF2* alteration was identified in a proband, available parents were screened systematically. Parents of 12 children were studied. For five of them, co-segregation with *TCF2* gene anomalies was consistent with dominant inheritance (Table 5). Subsequent clinical investigation showed that all *TCF2* gene anomaly–positive parents except one had renal abnormalities associated or not with diabetes or genital tract abnormalities (bilateral *via* deferens agenesis conducting to pregnancy by intracytoplasmic sperm injection). In seven other probands, the *TCF2* gene anomalies occurred *de novo* as their parents did not carry the corre-

Table 1. Antenatal characteristics of patients with ARPKD ($n = 12$)[a]

Patient	GA (wk)	AF	Family History	Perinatal Outcome	Kidney Length (SD)	Cysts	CMD
1	29	MOH	No	Alive	+3	No	P
2	26	SOH	No	TOP	+3	No	P
3	26	SOH	No	TOP	+3	No	P
4	22	MOH	ARPKD	TOP	+3	No	P
5	32	MOH	No	TOP	+4	No	P
6	22	SOH	No	TOP	+3	No	P
7	26	SOH	No	TOP	+2	No	P
8	28	SOH	No	TOP	+3	No	P
9	32	MOH	No	TOP	+3	No	P
10	22	MOH	No	TOP	+2	No	P
11	24	SOH	No	TOP	+3	No	P
12	32	SOH	No	ND	+4	No	P

[a]AF, amniotic fluid volume; ARPKD, autosomal recessive polycystic kidney disease; CMD, corticomedullary differentiation; GA, gestational age; MOH, moderate oligohydramnios; ND, neonatal death; P, poor; SOH, severe oligohydramnios; TOP, termination of pregnancy.

Table 2. Antenatal characteristics of patients with ADPKD ($n = 8$)[a]

Patient	GA (wk)	AF	Family History	Perinatal Outcome	Kidney Length (SD)	Cysts	CMD
1	32	N	ADPKD	Alive	+2	D, b, MC	NA
2	22	N	No	Alive	+3	No	N
3	24	SOH	No	TOP	+4	No	P
4	25	MOH	No	TOP	+3	No	N
5	21	N	ADPKD	Alive	+2	No	N
6	32	N	ADPKD	Alive	+2	No	NA
7	32	N	No	Alive	+2	D, u, MC	N
8	31	N	No	Alive	+2	No	N

[a]ADPKD, autosomal dominant polycystic kidney disease; b, bilateral; D, diffuse; MC, macrocysts; N, normal; NA, not available; PH, polyhydramnios; u, unilateral.

Table 3. Antenatal characteristics of patients with miscellaneous diseases ($n = 10$)[a]

Patient	GA	AF	Family History	Perinatal Outcome	Kidney Length (SD)	Cysts	CMD	Diagnosis
1	19	SOH	ARTD	TOP	+2	—	P	ARTD
2	33	SOH	No	TOP	+3	mc, D, b	P	Bilateral dysplasia
3	35	MOH	No	TOP	+3	mc, D, b	P	Type 2 Ivemark Sd
4	22	SOH	No	TOP	+2	mc, D, b	NA	Type 2 Ivemark Sd
5	32	N	No	Alive	+2	—	N	Familial nephroblastoma
6	22	N	No	Alive	+4	—	NA	BW syndrome
7	22	N	No	Alive	0	—	N	Transient HE
8	32	N	No	Alive	0	—	N	Transient HE
9	30	N	No	Alive	0	—	N	Transient HE
10	23	SOH	No	TOP	+3	mc, D, b	P	Type 2 Ivemark Sd

[a]ARTD, autosomal recessive tubular dysgenesis; BW, Beckwith-Wiedemann syndrome; b, bilateral; D, diffuse; HE, hyperechogenicity; mc, microcysts; Sd, syndrome.

sponding alteration; parental relationships were confirmed by testing a panel of 15 microsatellites (data not shown). In conclusion, large genomic rearrangements represent the large majority of the identified molecular anomalies in *TCF2* gene.

Renal Phenotype in Patients with TCF2 Anomalies

Prenatal Sonographic Evaluation (Table 5). Among the 18 patients with *TCF2* anomalies, the median gestational age at diagnosis was 26.0 ± 5.68 wk (range 18 to 35). Patients' disease was diagnosed mainly at 22 and 32 wk of gestation, corresponding to the systematic ultrasound performed during the second and the third trimesters. Kidney size was normal in all patients (between −1 and +2 SD) except in two siblings (patients 2 and sibling 2), who had enlarged kidneys (+3 SD) and a primary diagnosis of ADPKD. The mean kidney length was 0.5 ± 1.04 SD (0.18 ± 0.54 SD when patient 2 and sibling 2 were excluded). Amniotic fluid was normal in all cases (two with mild fluid excess).

The presence of antenatal cysts was observed in approximately half of the patients (11 [61%] of 18): Three had bilateral cortical microcysts, four had unilateral cortical microcysts, and four had unilateral diffuse macrocysts. In conclusion, two main antenatal phenotypes were found: (*1*) Bilateral, normal-sized, hyperechogenic kidneys with or without cortical microcysts (Figure 1) and (*2*) unilateral, normal-sized, hyperechogenic kidney with bigger contralateral kidney and diffuse macrocysts. Another imaging species was, in six of 18 cases, the presence of pelvic dilation, bilateral in two fetuses, and a horseshoe kidney (patient 12).

Postnatal Renal Functions and Sonographic Characteristics. After birth cysts appeared in all patients but one within the first year of life suggesting a progressive character of *TCF2* gene anomaly related renal phenotypes. Among the 7 patients without antenatal cysts, all but one developed cysts during the first year of life, bilaterally before the age of two years. For the children with antenatal renal cysts, the respective anomalies persisted on the postnatal sonographies with increase of cysts number and bilateral evolution in 8 patients. Improvement of pre-existing lesions was not observed during the follow-up (Table 6).

An important feature was the impaired kidney growth (Figure 2). The individual analysis of the renal unit growth showed, except for patient 2 and sibling 2, a decrease of the kidney height early in the first 2 yr of life. The mean antenatal kidney length was 0.5 ± 1.04 SD (0.18 ± 0.54 SD when patient 2 and

Table 4. Antenatal characteristics of patients with no acute diagnosis ($n = 28$)[a]

Patient	GA	AF	Renal Family History	Perinatal Outcome	Kidney Length R/L (SD)	Cysts	CMD	Diagnosis Others Anomalies
1[b]	32	N	No	Alive	0	—	N	—
S1[b]	32	N	No	Alive	0	—	N	—
2[b]	32	N	No	Alive	+3	mc, C, b	N	PD, b
S2[b]	32	N	No	Alive	+3	mc, C, b	N	PD, b
3[b]	22	N	No	Alive	+1	mc, C, u	N	—
4[b]	18	N	No	Alive	−1/+2	mc, C, u	N	PD, u
5[b]	22	N	No	Alive	0	—	N	—
6[b]	22	N	No	Alive	0	—	N	—
7[b]	20	N	No	Alive	+1/0	MC, D, u	P	PD, u
8[b]	22	N	No	Alive	0	—	N	—
9[b]	35	N	No	Alive	0	mc, C, u	P	PD, u
10[b]	32	N	No	Alive	0	MC, D, u	P	—
11[b]	31	PH	No	Alive	+1	—	N	—
12[b]	22	PH	CD	Alive	0	mc, C, b	N	HSK
13[b]	22	N	No	Alive	+1	[e]	N	—
14[b]	30	N	No	Alive	0/+1	MC, D, u	N	PD, u
15[b]	20	N	No	Alive	0/+2	MC, D, u	N	—
16[b]	22	N	No	Alive	0	mc, C, u	N	—
17	32	N	No	Alive	−1	—	NA	Renal hypodysplasia
18	21	N	No	Alive	+2	—	P	Dysplastic kidneys
19	30	N	No	Alive	+1/−1	mc, u	N	Dysplastic kidneys[f]
20[c]	22	SOH	No	TOP	+1	mc, C, b	N	Bilateral dysplasia[f]
21[c]	22	MOH	Dysplasia	TOP	+1	mc, C, b	N	Bilateral dysplasia[f]
22	34	N	No	Alive	0	mc, C, b	N	Cystic dysplasia + HE[f]
23	21	N	No	Alive	+1	mc, u	P	Isolated HE[f]
24	22	N	No	Alive	0	mc, u	N	Transient HE[f]
25	31	N	No	Alive	+1	mc, u	N	HE + cortical microcysts[f]
26[d]	32	N	No	Alive	0	—	N	PD, b

[a]C, cortical; CD, cystic disease; GCKD, familial glomerulocystic kidney disease; HE, hyperechogenicity; HSK, horseshoe kidney; L, left; PD, pelvic dilation; R, right; S, sibling.
[b]*TCF2* gene anomaly.
[c]Postmortem examination showed bilateral renal dysplasia with glomerular cortical and tubular microcysts, without hepatic and pancreatic dysplasia.
[d]Refused genetic exploration.
[e]Absence of cysts on ultrasonography but visible cysts on fetal magnetic resonance imaging (data not shown).
[f]Patients with negative *TCF2* analysis.

sibling 2 were excluded), and the mean postnatal renal length was −0.80 ± 1.61 SD (−1.28 ± 0.85 SD without patient 2 and sibling 2). Even in the case of involution of the multicystic dysplastic kidney, the contralateral kidney showed no compensatory hypertrophy.

The median age for the 18 patients at the last follow-up was 69.16 mo (range 6 to 180). The mean GFR was 65.82 ± 27,87 ml/min per 1.73 m^2. Seven patients have normal GFR (>70 ml/min per 1.73 m^2), eight have mild renal insufficiency (GFR <70 and ≥40 ml/min per 1.73 m^2), and three presented severe renal failure (GFR <40 ml/min per 1.73 m^2).

Urate values revealed elevated levels in nine patients and decreased levels in one patient with increased fractional urate excretion. Early uricemia in the first months of life was found in five patients (Table 7).

Postnatal Extrarenal Manifestations. A sonographic evaluation of the liver and the pancreas size was obtained in 16 and 10 patients with *TCF2* gene anomaly, respectively. No structural abnormalities were revealed. Magnetic resonance imaging (MRI) of the pancreas was performed in patient 2 and sibling 2, and pancreas hypoplasia was absent. Fecal elastase values were obtained in 10 patients, and a low value was found in patient 4 (93 μg/g for a normal value >150) even though no pancreas abnormalities were detected by sonographic evaluation (Table 7).

In all patients, fasting blood glucose and glycosylated hemoglobin levels ranged respectively from 3.6 to 5.8 mmol/L and 5 to 5.5% (normal values) except for patient 2, sibling 2, and patient 14, who developed diabetes. Patient 14 developed diabetes after renal transplantation at 12 yr of age. No anomalies were found in insulin blood levels. Liver enzyme levels (AST,

Table 5. Familial data for *TCF2*-positive patients[a]

Patient	*TCF2* Alteration	Familial Genetic Analysis	Renal Anomalies	Other Anomalies
1	DEL	DEL-F	Cystic solitary kidney + CRF	Bilateral *via* deferens agenesis
S1	DEL	DEL-F	Cystic solitary kidney + CRF	
2	DEL	NA	—	
S2	DEL	NA	—	
3	DEL	—	—	
4	DEL	—	—	
5	DEL	DEL-M	—	Cholestasis, uterus bicornis
6	DEL	—	—	
7	DEL	—	—	
8	DEL	—	—	
9	DEL	—	Bilateral cortical cysts + CRF	
10	DELex4	DELex4-F	NA	
11	DEL	NA	Bilateral cortical cysts	
12	MUT	MUT-M	—	
13	DEL	NA	Renal cysts	
14	MUT	—	—	Infertility
15	DEL	NA		
16	DEL	NA		

[a]CRF, mild chronic renal failure; DEL, heterozygous deletion of the complete *TCF2* gene; F, deletion in the father; M, deletion in the mother; MUT, mutation; NA, not available; —, no *TCF2* gene anomaly.

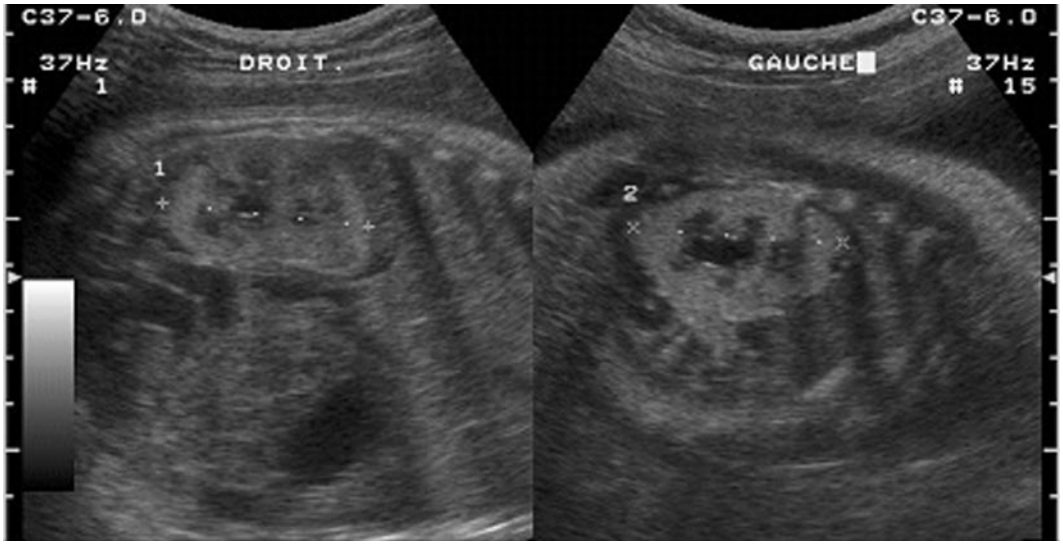

Figure 1. Prenatal echography at the 9th month of patient 9 (Table 5), who had two hyperechogenic kidneys of normal size (+1 SD).

ALT, or GGT) were two times higher than the upper limit in three patients. Serum triglyceride and cholesterol levels were available in 15 of 18 patients and were found to be normal.

Parental Phenotype. Subsequent clinical investigation showed that all parents except one, who received a diagnosed of a *TCF2* gene anomaly, had renal disease associated or not with diabetes or genital tract abnormalities (bilateral *via* deferens agenesis conducting to pregnancy by intracytoplasmic sperm injection). One parent had normal renal phenotype but liver dysfunction with elevated GGT activity and bicornis uterus. As in our pediatric cohort, we observed a large clinical variability among *TCF2* gene anomaly–positive parents and the absence of genotype–phenotype correlations (Table 5).

Table 6. Postnatal renal functions and morphology in patients with *TCF2* anomalies[a]

Patient (Gender)	Age at the Last Visit (mo)	Kidney Length R/L (SD)	HE	Cysts	Other Anomalies	GFR	Urate Level (μM/L)	Urate FE (%)
1(M)	24	0/−2	+	mc, C, b	PD	62.6	246	15
S1 (F)	24	−1/−2	+	mc, C, b	—	60	244	14
2 (F)	180	+3	+	MC, D, b	PD, b	39	440[b]	NA
S2 (F)	180	+3	+	MC, D, b	PD, b	46	434[b]	NA
3(M)	56	−1	+	mc, C, b	—	93.5	199	24
4(M)	22	−1/−3	+	mc, C, b	MCD, PD	63	244[b]	9.5
5(M)	30	−2	+	mc, C, b	—	93	388[b]	11
6 (F)	11	−1	+	mc, C, b	PD	70.5	339[b]	9
7(M)	20	0	+	mc, C, b[c]	IMCD	50	370[b]	9
8(M)	86	0	+	mc, C, b	—	95	278	12
9(M)	40	−1	+	mc, C, b	PD	111	367[b]	11.1
10 (F)	150	−1	+	mc, C, b[c]	PD, IMCD	38.5	451[b]	8
11(M)	48	−2	+	—	—	96	244	NA
12(M)	13	−2	+	mc, C, b	HSK	59.6	257[b]	14
13 (F)	6	0	+	mc, C, u	—	55	174	11
14 (F)	164	−2	+	mc, C, b[c]	IMCD	<10	422[b]	16
15(M)	41	−4/−1	+	MC, D, u	—	92	309[b]	11.3
16(M)	150	−3	+	mc, C, b	—	51	379	NA

[a]GFR is estimated using the Schwartz formula (ml/min per 1.73 m^2). Dilation of renal pelvis was defined as anteroposterior diameter >10 mm. F, female; FE, fractional excretion; IMCD, involuted multicystic dysplasia; M, male; MCD, multicystic dysplasia.
[b]High value.
[c]Cysts in solitary kidney because of involution of MCD.

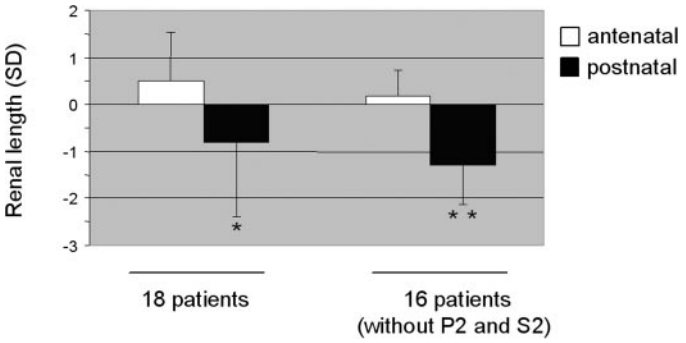

Figure 2. Evolution of the mean kidney length (SD) in patients with *TCF2* gene anomalies before (□) and after birth (■). *$P <$ 0.005, **$P < 0.0001$ using an unpaired *t* test compared with the antenatal value.

Discussion

The discovery of fetal bilateral hyperechogenic kidneys is very stressful for the pregnant woman and her family. For correct prenatal counseling, it is extremely important to put an accurate diagnosis, to measure the fetal renal function, and to predict postnatal renal adaptation. Increased echogenicity of the renal parenchyma is nonspecific and occurs in sclerosis, interstitial infiltration, and multiple cortical or medullary microcysts (28). Precise cause only on the basis of ultrasonographic data is almost impossible to establish in the absence of familial history. In all cases, ultrasonographic screening of the family is essential for the evaluation.

In this study, we report for the first time the incidence of *TCF2* gene anomalies in a large cohort of antenatally diagnosed bilateral hyperechogenic kidneys, and we show that *TCF2* anomalies are the main cause of antenatal hyperechogenic kidneys (29%). The prevalent genetic anomaly is the complete heterozygous deletion of the *TCF2* gene (83%). The presence of a heterozygous deletion seems to be associated with early fetal disease expression. Indeed, in a recent publication, only two thirds of the children with *TCF2* anomalies had a heterozygous deletion of the gene (22). Moreover, the complete *TCF2* deletion was found in one third of patients in a large cohort of adult patients with MODY5 (23). *TCF2* mutations are an important cause of adult renal disease; in a recent study, 23 different heterozygous HNF-1β mutations were found in 160 (14%) patients with various renal diseases, 40% of whom had a personal or family history of diabetes (16).

Family screening in our cohort showed that more than half of *TCF2* anomalies occurred spontaneously (seven of 12). In the case of *de novo TCF2* anomalies, the probability of recurrence is very low except in the presence of germline mosaicism. Forty-one percent of the *TCF2* gene anomalies in our cohort originated from autosomal dominant inheritance.

The wide clinical variability among *TCF2* patients and the absence of early genotype–phenotype correlations makes genetic counseling extremely difficult even when the autosomal

Table 7. Postnatal extrarenal manifestations in patients with *TCF2* anomalies[a]

Patient	Age at the Last Visit (mo)	Liver Function	Pancreatic Endocrine Function	Pancreatic Exocrine Function	Fecal Elastase (μg/g)
1	24	N	N	N	347
S1	24	N	N	N	263
2	180	N	Diabetes	NA	NA
S2	180	N	Diabetes	NA	NA
3	56	N	N	N	493
4	22	N	N	N	93[b]
5	30	×2	N	N	162
6	11	N	N	N	300
7	20	x2	N	N	293
8	86	N	N	N	367
9	40	N	N	N	409
10	150	N	N	N	NA
11	48	NA	NA	NA	NA
12	13	N	NA	N	NA
13	6	N	N	N	256
14	164	GGT×2	Diabetes	N	NA
15	41	N	N	NA	NA
16	150	N	N	N	NA

[a]NA, not available; ×2, more than two times the normal values for aspartate aminotransferase and alanine transaminase.
[b]Abnormal value.

dominant inheritance of *TCF2* mutations is diagnosed. Because of the high prevalence of large genomic deletions, the QMPSF analysis should be carried out as the first analysis in antenatal *TCF2* anomaly screening. Some antenatal characteristics seem to eliminate the possibility of *TCF2* anomalies: Oligohydramnios (none in our cohort), absence of corticomedullary differentiation and a kidney length more than + 3 SD (Table 5).

Among the 18 patients with a *TCF2*-linked pathology, only 11 (61%) had antenatally detected cysts, bilateral in three cases. Two main antenatal phenotypes were identified: (*1*) Bilateral, normal-sized, hyperechogenic kidneys with or without cortical microcysts or (*2*) a unilateral, normal-sized, hyperechogenic kidney with a larger contralateral kidney with diffuse macrocysts. These nonfunctional multicystic kidneys involuted at the last visit, and the contralateral kidney showed no compensatory growth. All of the others but one developed renal cysts after birth during the first year (94%), bilaterally in 15 (83%) of 18, suggesting a progressive character of *TCF2*-related renal phenotypes. For the children who received a diagnosis of hyperechogenic kidneys and cysts on antenatal sonography, the respective anomalies persisted on the first postnatal sonography and the number of cysts increased. However, improvement of preexisting lesions was not observed. At their last visit, the large majority (94%) of the *TCF2* patients in our cohort had renal cysts, confirming the results of a recent publication in which 84% of the children with *TCF2* anomalies had cortical cysts, bilateral in 64% (22). It is interesting that these cysts are located mainly in the renal cortex. The link between *TCF2* gene anomalies and the presence of cysts also was demonstrated recently in a pediatric cohort of 99 patients with renal hypodysplasia. In 27 patients with renal cysts, six (22%) had *TCF2* gene anomalies (29).

The use of prenatal MRI in patient 13 detected cortical microcysts that were invisible at sonography. Therefore, MRI analysis might allow better prenatal diagnosis in patients with antenatal hyperechogenic kidneys (30).

The presence of cortical or glomerular cysts is not specific of *TCF2* anomalies. In seven of the 25 patients, no *TCF2* gene anomaly was found with the presence of cortical cysts or glomerular cysts in histologic analysis. For patients 20 and 21, pregnancies were terminated because of the presence of severe oligohydramnios and increased fetal β2-microglobulin serum concentrations. The absence of *TCF2* gene anomalies might be explained either by genetic heterogeneity of the disease or other mutational mechanisms such as intronic variants located outside the coding sequence and exon/intron junctions that are missed by conventional screening method on genomic DNA. Patients for whom *TCF2* is negative should be studied for other candidate genes that lead to similar phenotypes.

The patient 2 and sibling 2, twins with a *TCF2* gene deletion, are very interesting. Fetal sonographies showed enlarged kidneys with diffuse cortical microcysts and normal amniotic fluid volume. After a long follow-up, their kidneys remained enlarged (+3 SD) with bilateral macrocysts (4 to 7 cm). A recent abdominal MRI confirmed the macrocysts with typical features of ADPKD (Figure 3). This is a different and more severe phenotype compared with the other *TCF2* gene deletions in our cohort. Although this remains to be established, the phenotype might be caused by an oligogenic origin of the pathology in these twins. On the basis of this observation, one also might

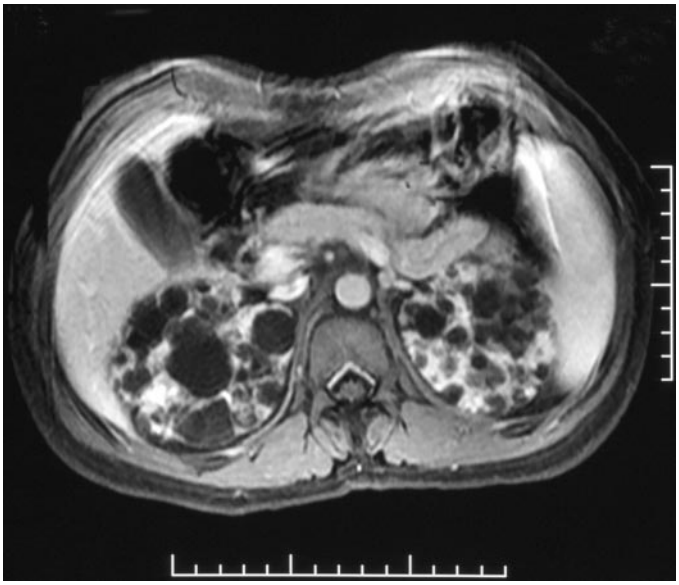

Figure 3. Renal magnetic resonance imaging showing enlarged kidneys (+3 SD) with diffuse bilateral macrocysts suggesting autosomal dominant polycystic kidney phenotype (patient 2).

consider looking for *TCF2* gene anomalies in patients 7 and 8 (Table 2).

The mechanism by which HNF-1β might be involved in the development of hyperechogenic kidneys in human is unknown. However, recent animal studies showed that HNF-1β interacts with *Pkd2* (polycystin 2); mice with renal-specific inactivation of HNF-1β develop PKD (31). Furthermore, it has been shown that HNF-1β directly controls the transcription of several genes that are expressed in the tubular epithelial cells: *Umod*, *Pkhd1* (polyductin), *Pkd2*, and *Polaris* (31–33). These genes all play a crucial role in cilium formation. Transgenic mice with a dominant negative HNF-1β mutant show decreased expression of Pkhd1 (32). These studies suggest the possibility that the mechanism of cyst formation in humans with mutations of HNF-1β involves downregulation of *PKHD1* gene transcription (32,33). These results obtained on animal models suggest that HNF-1β might be a major actor in cystogenesis.

Besides reporting for the first time the presence of a high prevalence of *TCF2* gene anomalies in antenatal hyperechogenic kidneys, we confirm the typical *in utero* presentation of ARPKD with enlarged hyperechogenic kidneys >2 SD with loss of corticomedullary differentiation, presumably as a result of the numerous small cysts that are undetectable by ultrasound and the constant decrease in amniotic fluid volume (1,2,21). These characteristics resulted in TOP in 10 of 12 cases and one neonatal death in our cohort. The sole surviving 3-yr-old child has hypertension, hepatic fibrosis, and chronic renal insufficiency (GFR <40 ml/min per 1.73 m^2).

Some characteristics seem more specific for ADPKD: The presence of cortical hyperechogenicity with hypoechogenic medulla, leading to an increased corticomedullary differentiation (34). Moreover, the cysts rarely are present in the fetuses (only two of eight in our cohort).

In all cases of antenatal hyperechogenic kidneys, the finding of severe oligohydramnios is ominous. Several data showed that enlargement of the kidneys >2 SD and severe oligohydramnios are predictive markers of poor renal function (1,2). However, the postnatal prognosis of renal dysplasia with normal amniotic fluid is very difficult to predict (35,36).

Serum β2-microglobulin values are not a good marker in the case of bilateral hyperechogenic kidneys because normal values cannot exclude postnatal renal failure. This marker is validated only in bilateral uropathies, bilateral renal hypoplasia, and dysplasia (2).

No conclusion concerning the course of the renal function in our *TCF2* cohort can be drawn to date. The impact of *TCF2* gene anomalies on renal function is not clear, and longer follow-up probably will enlighten this aspect. In our cohort, the degree of renal insufficiency was variable. Seven patients have normal GFR (>70 ml/min per 1.73 m^2), eight have mild renal insufficiency (GFR <70 and ≥40 ml/min per 1.73 m^2), and three present severe renal failure (GFR <40 ml/min per 1.73 m^2). The degree of renal insufficiency seemed related to the degree of hypo/dysplasia and therefore the degree of nephron loss.

When we compare our results with other data, the precocity of the diagnosis seems to be related to a poorer renal function. Ulinski *et al.* (22) found with a mean follow-up of 4.1 yr (0.3 to 18) that 56% of 25 patients with *TCF2* gene anomalies had a GFR >70 ml/min per 1.73 m^2, 40% had mild renal insufficiency (GFR between 40 and 70 ml/min per 1.73 m^2), and 4% had a GFR <40 ml/min per 1.73 m^2. The precocity of the diagnosis seems to be related with a poor renal function.

Because of the young age of many patients in our cohort and their insufficient follow-up, we were not able to define the annual individual decrease of GFR. Nevertheless, the patients with longer follow-up in our cohort or a sole functionary kidney and so presenting a nephronic reduction have the worse renal function. Taken together, both other studies and our data emphasize the severe renal prognosis that can be associated with *TCF2* gene anomalies but with a wide interindividual variability in renal outcome.

Because it has been shown that *TCF2* also is involved in the development of organs other than the kidney (4,5,14), we also studied extrarenal manifestations in our cohort. Three of the patients with *TCF2* anomalies developed diabetes. Patient 14 developed early end-stage renal failure at the age of 4. She underwent a renal graft at 10 yr of age and developed transitory diabetes just after transplantation with a recurrence 3 yr later. These observations should stimulate clinicians to explore endocrine pancreas function early in patients with *TCF2* anomalies before transplantation and to propose tailor-made antirejection therapies (*i.e.*, nondiabetogenic treatment). The varied spectrum of pediatric pathologies that are linked to HNF-1β is illustrated by the possibility of neonatal diabetes and early renal failure (18). Another benefit of MRI would be the visualization of pancreas and the search for pancreatic hypoplasia (14,23). A mouse model that lacks the *TCF2* gene showed anomalies in pancreatic development that result in pancreas agenesis (37).

Finally, biallelic inactivation of *TCF2* (combination of a germ-

line mutation and a somatic gene deletion [37]) can lead to chromophobe renal cell carcinoma in adults. The *TCF2* gene acts as a tumor suppressor during carcinogenesis of chromophobe renal cell carcinoma (38,39). One can wonder about the chances of our patients to develop cancer in the coming few years.

Conclusion

This first study with antenatally diagnosed bilateral hyperechogenic kidneys provides further insights into the early and complex molecular events that are involved in renal dysplasia with or without cysts. Antenatal *TCF2* gene anomalies have been shown to be the most important genetic anomalies related to isolated bilateral hyperechogenic kidneys. We identified *TCF2* gene anomalies in 18 patients; complete gene deletion occurred in 15 of them. Our antenatal *TCF2* anomaly–diagnosed pediatric cohort will allow us to perform a long-term prospective follow-up to determine phenotypic particularities in both renal and extrarenal sites, thereby allowing better prenatal counseling.

Disclosures

None.

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